Remarks/Arguments

Claims 39 - 44 are pending in this application, and stand rejected on various grounds. The present rejections to the claims are respectfully traversed.

Response to Arguments

Applicants gratefully acknowledge the Examiner's withdrawal of the rejection under 35 USC 112, second paragraph and indication that the term "specifically binds" as used in the claims is not indefinite.

Response to Amendment

The Examiner has indicated that the declaration filed under 37 CFR 1.132 filed February 19, 2003 is insufficient to overcome the rejection of claims 39-44 based upon 35 USC 101 and 112, first paragraph. The Examiner acknowledges that real-time PCR is a reliable means of determining gene copy number in cells or tissues. However, the Examiner states that there are utility and enablement issues of aneuploidy and antibody vs DNA which were not resolved by the declaration.

Applicants enclose herewith a Declaration by Avi Ashkenazi, Ph.D., an expert in the field of cancer biology. For the reasons set forth below , based on the statements in the Declarations of Audrey Goddard (previously submitted) and Avi Ashkenazi, Applicants maintain that the claimed invention is supported by a specific, substantial and credible utility and is fully enabled.

35 U.S.C. § 101 Utility Rejection

Claims 39 - 44 stand rejected under 35 USC §101 because the claimed invention is allegedly not supported by either a credible, specific and substantial asserted utility or a well established utility.

A Declaration under 37 C.F.R. 1.132 by Dr. Goddard was previously filed supporting that the TaqMan™ PCR technique is technically sensitive enough to detect at least a 2-fold increase in gene copy number relative to control. Dr. Goddard concludes that a gene identified as being amplified at least 2-fold by the quantitative TaqMan™ PCR assay in a tumor sample is useful as

a marker for the diagnosis of cancer, for monitoring cancer development and/or measuring the efficacy of cancer therapy.

The Examiner states that even though in some circumstances and as discussed in the Goddard declaration, TaqMan™ real-time PCR can accurately and reproducibly assess gene amplification, in cancerous tissues, it is necessary to account for the possibility of aneuploidy.

This rejection is traversed for the following reasons. Applicants have enclosed a Declaration by Avi Ashkenazi, Ph.D., an expert in the field of cancer biology. In his declaration, Dr. Ashkenazi confirms that amplification of a cancer marker gene - as detected, for example by the reverse transcriptase TaqMan™PCR or the fluorescence *in situ* hybridization (FISH) assays - is useful in the diagnosis or classification of cancer, or in predicting or monitoring the efficacy of cancer therapy.

He states:

> "An increase in gene copy number can result not only from intrachromosomal changes but also from chromosomal aneuploidy. It is important to understand that detection of gene amplification can be used for cancer diagnosis even if the determination includes measurement of chromosomal aneuploidy. Indeed, as long as a significant difference relative to normal tissue is detected, it is irrelevant if the signal originates from an increase in the number of gene copies per chromosome and/or an abnormal number of chromosomes"

Accordingly, aneuploidy does not need to be controlled for and clearly the results disclosed in the present application are significant.

The Examiner also rejects the claims for lack of utility allegedly because even assuming the DNA had utility as a lung and colon tumor marker, the encoded protein and its cognate antibody would not have utility because it is not known what the protein does or if the level of protein in tumors corresponds to nucleic acid transcript level. Citing Pennica *et al.* and additionally Haynes *et al*,. the Examiner states that protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript. Therefore, because it allegedly cannot be concluded that the PRO339 is useful as a diagnostic marker for colon or lung cancer, neither the protein nor antibody that specifically binds it has utility.

For the following reasons, Applicants respectfully disagree.

Evidentiary Standard

An applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re* Langer, 503 F.2d 1380,1391, 183 USPQ 288, 297 (CCPA 1974). See, also *In re* Jolles, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re* Irons, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977).

Compliance with 35 U.S.C. § 101 is a question of fact. Raytheon v. Roper, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration. In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992) Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Only after the Examiner made a proper *prima facie* showing of lack of utility, shifts the burden of rebuttal to the applicant. The issue will then be decided on the totality of evidence.

A prima facie case of lack of utility has not been established

The Examiner bases the conclusion of lack of utility on a quote from Pennica *et al.*, submitted as Exhibit D of the Goddard Declaration filed with applicants' response to the prior Office Action. According to the quoted statement, WISP-1 gene amplification in human colon tumors correlated with over-expression; WISP-3 RNA was over-expressed in the absence of gene amplification; and WISP-2 DNA was amplified in colon tumors, while its mRNA was reduced in the majority of tumors. The Examiner also relies on Haynes *et al.* who studied 80 proteins in the yeast *Saacharomyces cerevisiae* growing at mid-log phase. The Examiner states that Haynes *et al.* found no strong correlation between protein and transcript levels. From this, the Examiner correctly concludes that increased copy number does not *necessarily* result in increased protein expression. The standard, however, is not absolute certainty. The fact that in the case of a specific class of closely related molecules, WISP polypeptides, there seemed to be no correlation with gene amplification and the level of mRNA/protein expression, does not establish that it is

more likely than not, in general, that such correlation does not exist. Indeed, the working hypothesis among those skilled in the art is that, if a gene is amplified in cancer, the encoded protein is likely to be expressed at an elevated level. Furthermore, in the passage cited by the Examiner in Haynes, Haynes actually states, "Thus far, we have found a general trend but no strong correlation between protein and transcript levels". Thus Haynes supports the general trend that protein levels correspond to transcript levels.

Even if a prima facie case of lack of utility had been established, it should be withdrawn on consideration of the totality of evidence

Even if one assumes arguendo that it is more likely than not that there is no correlation between gene amplification and increased mRNA/protein expression, a polypeptide encoded by a gene that is amplified in cancer would still have a specific and substantial utility.

As Dr Ashkenazi explains in his Declaration,

> even when amplification of a cancer marker gene does not result in significant over-expression of the corresponding gene product, this very absence of gene product over-expression still provides significant information for cancer diagnosis and treatment. Thus, if over-expression of the gene product does not parallel gene amplification in certain tumor types but does so in others, then parallel monitoring of gene amplification and gene product over-expression enables more accurate tumor classification and hence better determination of suitable therapy. In addition, absence of over-expression is crucial information for the practicing clinician. If a gene is amplified but the corresponding gene product is not over-expressed, the clinician accordingly will decide not to treat a patient with agents that target that gene product.

Accordingly, the PRO339 polypeptide and antibodies binding to it have a substantial specific utility, and the present rejection should be withdrawn.

35 U.S.C. §112, First paragraph,Rejections

Claims 39-44 stand rejected under 35 USC 112, first paragraph for lack of enablement because the claimed invention allegedly is not supported by a credible, specific and substantial asserted utility, hence one skilled in the art clearly would not know how to use the claimed invention.

In response to the previous rejection under 35 USC 101, Applicants have shown that the specification discloses a substantial, specific and credible utility for the PRO339 polypeptide or antibodies against it. Applicants respectfully submit that it would not require undue experimentation for one of skill in the art to apply the teachings of the present disclosure so as to practice the invention by using antibodies that specifically bind to the polypeptide shown in Figure 118 (SEQ ID NO:339). Accordingly, the Examiner is respectfully requested to reconsider and withdraw the rejection of all pending claims.

Claim Rejections - 35 U.S.C. § 102(a)

Claims 39-44 stand rejected under 35 USC 102(b) as being anticipated by (WO99/63088). because WO99/63088 teaches antibodies to PRO1281 (Figure 233) including bispecific antibodies wherein the antibody binds PRO1281 and an other antigen (p.368, line 21,- p. 370, line 13), that would for reasons of records allegedly be reasonably expected to bind the polypeptide of SEQ ID NO:339 of the instant application.

The Examiner, in supporting the rejection, refers to p. 74, lines 34-35 of the specification which refers to epitope tagged polypeptides. The Examiner notes that the specification states that suitable tag polypeptide generally have at least six amino acid residues and usually between about 8 and 50 amino acid residues. The Examiner further notes that WO99/63088 has a region of 18 contiguous amino acids identical to SEQ ID NO:339 and multiple regions of at least 6 contiguous amino acids. (It is presumed that the Examiner means that PRO1281 found in WO99/63088 has these regions of identity).

The Examiner further states that an antibody that specifically binds is generally understood by those of skill in the art to bind with specificity to the identified polypeptide, but may cross-react, binding to a lesser extent with other polypeptides. Accordingly, absent evidence to the contrary, the WO99/63088 allegedly would be reasonably expected to bind the polypeptide with the sequence of SEQ ID NO:339 because the proteins share large regions of high identity.

This rejection is traversed for the following reasons.

First, the section at page 74 referenced by the Examiner describes epitope tagged chimeric polypeptides comprising a PRO polypeptide fused to a "tag polypeptide". The specification states "(s)uitable **tag polypeptides** generally have at least six amino acid residues and usually

between about 8 and 50 amino acid residues. Accordingly, it is the **tag polypeptide** and not the PRO polypeptide which is at least 6 amino acids or between 8 - 50 amino acids. Therefore, the passage quoted by the Examiner does not refer to the PRO polypeptide.

Second, the Examiner simply states that it is generally understood that an antibody that "specifically binds" may cross-react to a lesser extent with other polypeptides. The Examiner offers no support for this statement. Accordingly, the patent office has not met its burden of proof. Applicants assert that the generally accepted meaning of the phrase "specifically binds" is that the antibody binds specifically to the identified polypeptide **and to no other polypeptide**. Stedman's Medical Dictionary (copy enclosed) defines specfic as: "In immunology, having an affinity limited to a particular antibody or antigen". Thus an antibody that binds to both the PRO339 polypeptide of this application and to polypeptide PRO1281 of WO99/63088 would not be within the scope of the present claims. Thus Applicants maintain that the claimed invention is not anticipated by WO99/63088. Accordingly, withdrawal of the present rejection is requested.

Rejection under 35 U.S.C. § 103

1. Claims 39-44 stand rejected under 35 USC 103(a) as being unpatentable over GenBank Accession No. BAA92640 in view of Sibson *et al.* (WO94/01548) and Godowski *et al.* (U.S. Patent No. 6,030,831) for the reasons set forth in the previous Office Action (paper 11) and because it allegedly would have been obvious to one of ordinary skill to make an antibody including a bivalent antibody to the polypeptide of GenBank Accession No. BAA92640 because Sibson *et al.* outlines the uses advantages and general methods of making antibodies to protein encoded by expressed nucleic acids and Godowski *et al.* teaches a variety of antibody types including bivalent antibodies and methods of making them..

2. Claims 39 - 44 stand rejected under 35 USC 103(a) as being unpatentable over GenBank Accession No. BAA92640 in view of Applicants' admission on p. 34, lines 5-6 and Fleming et al. (Dev, 124:2973-81, 1997) and Godowski et al. (U.S. Patent No. 6,030,831) for the reasons set forth in the previous Office Action (paper 11) and because it allegedly would have been obvious to one of ordinary skill to make an antibody, including a bivalent antibody, to the polypeptide of GenBank Accession No. BAA92640 because Fleming et al. teach a secreted

protein, fringe, which Applicants admit is structurally related to PRO339 and because Godowski et al. provide the necessary routine methods to and motivation for making bivalent antibodies..

Applicants traverse these rejections for the following reasons. Applicants have claimed priority to International Application PCT/US00/03565, filed February 11, 2000. Accordingly GenBank Accession NO. BAA92640 is not prior art against the instant application.

In the Office Action, the Examiner argues that the instant subject matter lacks the necessary support for priority under 35 USC 112 because the claims do not have specific and substantial utility. As will be apparent from the discussions above and the Declarations by Dr. Goddard and Dr.Ashkenazi filed under 37 C.F.R. §1.132, Applicants submit that the results of the gene amplification assay (Example 92) provide specific and substantial asserted utility for the polypeptide PRO339. These results (Example 92) were first disclosed in PCT/US00/03565. Accordingly, the effective filing date of this application is February 11, 2000 and the claims pending are fully entitled to the priority of February 11, 2000.

Accordingly GenBank Accession NO. BAA92640 is not prior art against the instant application. The other references cited do not provide the disclosure of the sequence of BAA92640 and accordingly the claim invention is not obvious in light of the combination of the other references. Withdrawal of these rejections is respectfully requested.

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited. Applicants have enclosed a Notice of Appeal to maintain the pendancy of the application.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641**, referencing Attorney's Docket No.: **39780-1618P2C51**. Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: October 2, 2003

By: _____
Leslie A. Mooi (Reg. No. 37,047)

HELLER EHRMAN WHITE & McAULIFFE LLP
Customer No. 35489
275 Middlefield Road
Menlo Park, California 94025
Telephone: (650) 324-7000
Facsimile: (650) 324-0638

SV 458521 v2
10/2/03 1:40 PM (39780.1618)